D2

activate prostate antigen specific T cells compared to the number of dendritic cells in a cell population directly isolated from peripheral blood.

REMARKS

Claims 23, 24, 26 and 28-37 have been examined in the present application. Applicants have amended claims 23 and 31 to set forth the invention with greater particularity as described in greater detail below. All amendments are supported by the specification as filed and no new matter has been added. Applicants respectfully request reconsideration of the pending claims in light of the claim amendments above and the following remarks.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 23, 24, 25 and 28-37 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is not nearly connected, to make and/or use the invention. In particular, the Examiner does not believe the phrase "dendritic cell competent and enabled to activate T cells" is supported by the specification wherein dendritic cells competent and "able" to activate T cells are disclosed.

Although Applicants do not believe the phrase as used in this context would be construed differently, claims 23 and 31 have been amended to substitute "able" for "enabled". This substitution is not believed to limit the claim scope in any way.

Claims 23, 24, 26 and 28-37 also stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner apparently believing the claims to be enabled for human dendritic cells competent and able to activate T cells specific for a prostate antigen wherein the prostate antigen is a lysate of LNCaP cells. It appears the Examiner does not believe this disclosure is sufficient to enable claims where the prostate antigen is a prostate tumor lysate. In particular, the Examiner states that "[i]t is of little practical use for human dendritic cells [are] competent and able to activate T cells specific for a

prostate antigen, wherein the prostate antigen is a lysate of LNCaP cells, because the antigen present on the surface of LNCaP and recognized by T cells could be different and does not exist in primary prostate tumor cells." The Examiner, goes on to cite and summarize several references including Drexler *et al.*, *Leukemia and Lymphoma* 9:1-25(1993), Embleton *et al.*, *Immunol. Ser.* 23:181-207(1984), Hsu (*in*, *Tissue Culture Methods and Application*, Kruse and Patterson, eds., 1973, Academic Press, NY, p. 764) and Freshneg (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc. (1983), New York, p. 4) to support the proposition that cultured tumor cell lines are different than primary tumor cells and that care must be taken when interpreting results obtained with cultured tumor cell lines. Further, the Examiner concludes that "based on the cell culture data presented in the specification, it could not be predicted that primary prostate tumor cells have the same surface antigens as LNCaP cells" and that one of skill in the art would require undue experimentation to practice the claimed invention.

Applicants respectfully traverse this rejection. As above Applicants would like to thank the Examiner for granting the 27 February 2002 interview. During the interview several references were discussed, including Horoszewicz *et al.*, in, *Models for Prostate Cancer* (1980), pp. 115-132, Horoszewicz *et al.*, U.S. 5,162,504 and Simons *et al.*, *Cancer Res.* 59:5160-5168 (1999). As discussed briefly in the interview, Applicants agree that tumor cell lines are not identical to primary tumor cells for some specific purposes, but for the present invention all that is required of a model prostate cancer cell line is that the cell line share antigens with primary prostate cells and that the antigens in common with the line are capable of providing a target for cell killing (or lysis) by cytotoxic T lymphocytes. It is well known to the practitioner in the immunology art that LNCaP cells do share common antigens, such as, prostate specific antigen, prostate specific membrane antigen and prostatic acid phosphatase, and the like, with primary prostate tumor cells. To support this point three references were provided to the Examiner for the interview that clearly teach that LNCaP cells share antigens with prostate cells, including, at least, prostatic acid phosphatase (PAP), prostate specific membrane antigen (PSMA), and a 150 kd polypeptide recognized by sera from men

treated with an autologous prostate cancer antigen vaccine. Both PAP and PSMA are targets for various diagnostic tests and are being used in the design of several treatment modalities for prostate cancer either currently available commercially or in development, including human clinical trials.

In addition, the specification as filed provides evidence for the stimulation of prostate specific T cells by dendritic cells presenting purified prostate specific membrane antigen. See page 26, lines 13-14. This experiment is described as providing even better results in stimulating CTL than LNCaP cell lysate. Therefore, Applicants believe that one of skill in the art, without undue experimentation, can practice the present invention using any antigen on prostate and prostate tumor cells.

Rejections Under 35 U.S.C. § 112, Second Paragraph:

Claims 23, 24, 26 and 28-37 stand rejected under 35 U.S.C. § 112, second paragraph, the Examiner believing the claims are indefinite for the use of the phrase "T cells to a prostate antigen." In particular, the Examiner believes it is not clear what "T cells to a prostate antigen" are. The Examiner has suggested the use of the phrase, "T cell specific to a prostate antigen."

Although Applicants believe that one of skill in the art would understand the meaning of the phrase in question and in order to further expedite prosecution, claims 23 and 31 have been amended to recite "T cells specific to a prostate antigen" as suggested by the Examiner. Applicants do not believe that the amendment is limiting and a full range of equivalents should be retained as the two phrases are believed to mean the same thing within the context of the invention.

Claims 23, 24, 26 and 28-37 further stand rejected under 35 U.S.C. 112, second paragraph, the Examiner believing that it is unclear how one can distinguish the dendritic cells isolated from the claimed method and those "directly" isolated from peripheral blood. Further, the Examiner believes the claims are confusing because it is not clear what amount of peripheral blood is used for isolating the claimed dendritic cells versus the amount of peripheral blood for "drafting" isolated dendritic cells.

Although Applicants believe claims 23, 24, 26 and 28-37 are sufficiently clear as required under 35 U.S.C. § 112, second paragraph, particularly in light of the specification, claims 23 and 31 have been amended to clarify and to point out the invention with greater particularity. The claims have been amended to insert the phrase "a cell population" to further describe the human dendritic cells competent and able to activate T cells specific to a prostate antigen. The cell population contains an increased number of human dendritic cells competent and able to activate cytotoxic T cells specific to a prostate antigen because the method disclosed in the present invention provides for the isolation and enriched of immature monocytic dendritic cell precursors from peripheral blood. The enriched immature monocytic dendritic cell population are then contacted with prostate antigen in the form of, for example, LNCaP cells, LNCaP cell lysate, LNCaP cell membrane, tumor cells isolated from patient, tumor cell lysate, tumor cell membranes, purified prostate specific membrane antigen, *i.e.*, PSMA, or peptides from PSMA as set forth in the specification. This enriched dendritic cell population exposed to prostate antigen comprises an increased number of human dendritic cells competent and able to activate T cells specific to prostate antigen as compared to a similar dendritic cell population directly isolated from peripheral blood that has not been exposed to prostate antigen and allowed to mature (directly isolated). The enriched dendritic cell population that is not exposed to antigen will have only a few or possibly no dendritic cells competent and able to activate T cells specific to prostate antigen. As the increased number of dendritic cells competent and able to activate cytotoxic T cells specific to a prostate antigen is a relative number depending on the overall population size the actual amount of blood used to derive the cells is not relevant to the clarity of the claims.

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 23, 24, 26 and 28-37 under 35 U.S.C. § 112, second paragraph, in light of the amendments to claims 12 and 31, and the above remarks.

Rejections Under 35 U.S.C. § 102:

Claims 23, 24 and 31-36 stand rejected as being anticipated by Cohen *et al.*, (of record), as evidenced by Sallusto *et al.* (of record), Koch *et al.*, *J. Immunol.* 155:93-100 (1995), and Czerniecki *et al.*, *J. Immunol.* 159:3823-3827(1997). The Examiner believes that one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen would process and present antigen similarly to dendritic cells exposed to cytokines as evidenced by Sallusto *et al.* Further, the Examiner cites to Example 2 of Cohen as demonstrating that the dendritic cells that result from the process described can successfully reduce prostate tumor size. Also, the Examiner believes Applicants have misinterpreted the word "activated" dendritic cells. In analyzing the Cohen reference the Examiner has concluded that the treatment of the monocyte and dendritic cells precursors obtained by the process described by Cohen with calcium ionophore gives the same result as exposure cytokines as described, for example, by Sallusto *et al.* Applicants again respectfully traverse this rejection.

Applicants and Applicant's representative thank the Examiner for granting the 27 February 2002 interview and providing an opportunity to distinguish the present invention from the Cohen reference. As discussed in the interview and previously argued the dendritic cells of Cohen following treatment with calcium ionophore are incapable of processing antigen because they are in fact mature dendritic cells. As additional support for this position, Applicants provided to the Examiner for discussion during the interview and further consideration, Zhou and Tedder, *Proc. Nat'l. Acad. Sci. USA* 93:2588-2592(1996) and Koski *et al.*, *Blood* 94:1359-1371 (1999). Briefly, Zhou and Tedder describe the phenotypic and morphologic characteristics of plastic-adherent blood monocytes cultured in certain cytokines, including GM-CSF and IL-4 with or without TNFα. Only those plastic-adherent cells cultured in GM-CSF, IL-4 and TNFα displayed the characteristics of mature dendritic cells including expressing the $CD83^+$ phenotype. See, for example, Figure 1 and the Discussion Section.

Koski *et al.*, is an additional report from the Cohen Laboratory providing additional characterization of human peripheral blood monocyte and dendritic cells

treated with calcium ionophore. The abstract summarizes the laboratories previous reports as "leading to monocytes and dendritic cells to the rapid (18 hour) acquisition of many characteristics of mature DC, including CD83 expression." As previously argued and discussed in the interview the dendritic cells of Cohen following calcium ionophore treatment are mature dendritic cells. Mature dendritic cells as demonstrated by Zhou and Tedder and Sallusto are incapable of processing antigen. Therefore, Example 2 of Cohen is merely prophetic and can not enable a dendritic cell population as set forth in pending claims.

In view of the above remarks Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 23, 24, and 31-36 under 35 U.S.C. § 102(e) as being anticipated by Cohen *et al.*

Rejections Under 35 U.S.C. § 103:

Claim 26 stands rejected under 35 U.S.C. § 103 as unpatentable over Cohen *et al* in view of Lutz for the reasons already of record. Briefly, the Examiner believes Cohen *et al.* teaches the dendritic cells population of the claims, but fails to teach extended life span dendritic cells. Lutz *et al.* is believed by the Examiner to teach making immortalized dendritic cells to allow for *in vitro* culture for long periods of time.

Applicants must again traverse this rejection. As above, Cohen *et al.* does not disclose the presently claimed invention. Therefore, Lutz *et al.* adds nothing to render obvious the immortalized dendritic cells, *i.e.,* expanded life span or immortalized dendritic cells, of the invention. It is respectfully requested that the Examiner reconsider and withdrawn this rejection.

Claims 28 and 29 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Cohen *et al.* in view of Taylor *et al.*, because the Examiner believes that it would be obvious to use the cryopreservation techniques of Taylor *et al.* to preserve the dendritic cells of Cohen *et al.* Further, the Examiner believes that one of ordinary skill in the art would have expected that the dendritic cells would have remained functional following cryopreservation.

Applicants respectfully must again traverse this rejection. As above, the dendritic cell population of the present invention as set forth in claim 23 is not the same as that described by Cohen *et al.* and is therefore patentably distinct. Claims 28 and 29, dependent on claim 23, are therefore also not obvious in view of the cited references. In fact, claim 23 being patently distinct renders to rejection moot as there can be no suggestion in the references for their combination as suggested by the Examiner. It is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 28 and 29 under 35 U.S.C. § 103 as obvious over Cohen *et al.* in view of Taylor *et al.* in light of the above remarks and the interview.

Claim 30 stands rejected under 35 U.S.C. § 103 as obvious over Cohen *et al.* in view of Taylor *et al.*, and further in view of Lutz *et al.*, for reasons previously set forth. Briefly the Examiner described, Cohen *et al.*, as teaching the same population of dendritic cells claimed in the present application and that Lutz *et al.* allegedly provided the immortalization techniques to the dendritic cells taught by Cohen *et al.* which had been cryopreserved by the techniques of Taylor *et al.*

As above, the dendritic cell population of the present invention are not the same as those of Cohen *et al.* Therefore, no motivation to combine the references is present in the references themselves. Claim 23 is novel and not anticipated or obvious over Cohen *et al.*, therefore a claim dependent thereon is also novel and is not obvious over the same combination of references. Applicants respectfully request reconsideration of claim 30 in light of the above remarks.

Claim 37 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Cohen *et al.* in view of Stites *et al.*, *Basic and Clinical Immunology*, 1991, pp. 45. The Examiner believing that Cohen *et al.* teaches the same dendritic cell population as claimed in the present invention, but does not teach the use of dendritic cells isolated from normal individuals that are HLA-matched for the recipient. It is alleged that Stites *et al.* teaches the matching of HLA antigens as important and that it would have been obvious to one of skill in the art at the time the invention was made to match HLA of dendritic cells of a donor for a recipient with a reasonable expectation of success.

As with the other claims dependent on claim 23, claim 37 is indirectly dependent and is therefore not anticipated in view of or obvious over Cohen *et al.* The dendritic cell population is not the same as discussed above. There is also no motivation to combine the references to render obvious the invention encompassed by claim 37. As the dendritic cell population of claim 23 is novel and not obvious over the primary reference (Cohen *et al.*) and no motivation is provided in the references for their combination to suggest the presently claimed invention, the dependent claim, claim 37, is also not obvious. Therefore, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 37 under 35 U.S.C. § 103(a) as obvious over Cohen *et al.* in view of Stites *et al.*

Applicants believe the claims pending in the present application are not obvious over the any of the cited art either individually or in any combination as set forth by the Examiner above. It is respectfully requested the Examiner reconsider and withdraw all of the rejections under 35 U.S.C. § 103 in view of the remarks set forth above.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If however, the Examiner believes a telephone conference would aid in the prosecution of this application in any way, please call the undersigned at 206-467-9600.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Four Times Amended) A composition comprising a cell population having an increased number of human dendritic cells competent and [enabled] able to activate T cells specific to a prostate antigen as compared to [those]a cell population directly isolated from peripheral blood.

31. (Amended) The composition according to claim 23 comprising a cell population having at least 20 fold more dendritic cells competent to and [enabled]able to activate prostate antigen specific T cells compared to the number of dendritic cells in a cell population directly isolated from peripheral blood.